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(PHARMACEUTICAL BULK SUBSTANCES)

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(54) Abstract Title: Kit for preparing a formulation of paclitaxel

(57) A kit for preparing a pharmaceutical formulation of Paclitaxel, whereby the individual ingredients are supplied in separate, sterilely sealed containers. The formulation is chemically, pharmaceutically, and also microbiologically stable.

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This print incorporates corrections made under Section 117(1) of the Patents Act 1977.

Kit for Preparing a Formulation of Paclitaxel

The invention relates to a kit for preparing a pharmaceutical formulation of Paclitaxel.

Paclitaxel is a naturally occurring compound which can be isolated from yews or yew bark. The active substance posse sses cytostatic and cytotoxic properties and is the main ingredient of pharmaceutical products used in cancer therapy.

Treatment with Paclitaxel has, for example, been described for ovarian cancer (cf. inter alia, McGuire et al., Ann. Int. Med. 111, 273 -279 (1989)), breast cancer (cf. inter alia, Holmes et al., Proceedings of the American Society of Clinical Oncology, Vol. 10, p. 60), lung cancer (cf. inter alia, Brown et al., J of Clin Oncol, Vol. 9, No. 7, pp. 1261-1267), and leukemia (cf. inter alia, Ro winsky et al., Cancer Research 49, 4640-4647).

Paclitaxel itself is not readily soluble in water, so it is difficult to prepare a proper formulation which can then be further diluted with aqueous infusion solutions (e.g. 0.9% NaCl solution). Furthermore, because of its responsivity to water and alkalis, Paclitaxel is also not sufficiently stable in lipophilic solvents, e.g. polyethoxylated castor oil, such as Cremophor EL® or Cremophor ELP®, or in alcoholic solvents, such as ethanol.

The problem behind the invention is to supply Paclitaxel in such a way that the aforementioned stability problems are avoided and the form of preparation necessary for administration to the patient can be prepared quickly and simply.

The problem of the invention was solve d by developing a kit for the preparation of a form with a defined composition which can be administered as a pharmaceutical.

Thus, the object of the invention is a kit for the preparation of a pharmaceutical formulation of Paclitaxel, characterized in th at a defined quantity of Paclitaxel is supplied in one sterilely sealed vial, a defined solution of citric acid anhydride in ethanol (solution A) in a second sterilely sealed vial, and a defined solution of Cremophor EL® or Cremophor ELP® in absolute ethanol (solution B) in a third sterilely sealed vial.

The medication prepared with this method represents a clearly cost -effective alternative to the manufactured pharmaceutical products currently on the market with the ingredient Paclitaxel.

Stability problems during lengthy storage of the solution are avoided by supplying the active substance, the solvent, and the stabilizer separately. The dissolved form of the active substance is prepared immediately before its use by the pharmacist or doctor.

The active substance Paclitaxel is supplied in a precisely defined quantity in the first sterilely sealed vial.
The vial is appropriately sized to take in corresponding quantities of solution A and solution B during the preparation of the solution.

The active substance Paclitaxel is present in the first vial in a precisely defined quantity. This allows the preparation of, for example, exactly 30 mg, 100 mg, 300 mg, 500 mg, 1000 mg, 2000 mg, 3000 mg, or more of Paclitaxel.

Paclitaxel is only dissolved when shaken after a defined quantity of solution A has been added. It is not normally necessary to heat the mixture; however, the mixture may be heated by the warmth of the preparer's hands in order to accelerate the dissolution process.

Solution A consists of anhyd rous citric acid (or citric acid anhydride) and absolute ethanol, whereby 970 mg of citric acid (or citric acid anhydride) are dissolved in 70.6 mg of absolute ethanol (=89.4 ml).

A defined quantity of solution B is then added, and the mixture is shaken u ntil the solution becomes homogenous.

Solution B consists of a mixture of Cremophor EL ® or Cremophor ELP® (BASF Company), which has also been purified by hypercritical fluids if necessary, whereby 258.8 mg of Cremophor and 123.5 mg of ethanol (=156.4 ml) are present in the vial.

The vials are made of glass or a chemically inert material and are sterilely sealed.

3 ml of solution A and 14 ml of solution B are used per 100 mg of Paclitaxel. Multiples or fractions of these solvents are used as appropriat e for the larger quantities of Paclitaxel indicated above.

The formulation of Paclitaxel prepared in this manner is chemically, pharmaceutically, and also microbiologically stable for at least one year.

Additional preparation for infusion into the patien t is performed by diluting the Paclitaxel concentrate prepared in this manner with the usual infusion solutions.

Example 1:

3 ml of solution A are added to 100 mg of Paclitaxel in the first vial, and Paclitaxel is dissolved in this solution by shaking. 14 ml of solution B are then added, and the mixture is shaken until it is homogenous.

The concentrate can now be processed further to prepare an infusion solution.

It is also possible to store this Paclitaxel concentrate for at least 1 year.

Example 2:

9 ml of solution A are added to 300 mg of Paclitaxel in the first vial, and Paclitaxel is dissolved in this solution by shaking. 52 ml of solution B are then added, and the mixture is shaken until it is homogenous.

The concentrate can now be processed fur ther to prepare an infusion solution.

It is also possible to store this Paclitaxel concentrate for at least 1 year.

Patent Claims:

1) Kit for the preparation of a stable pharmaceutical formulation of Paclitaxel, characterized in that a defined quantity of Paclitaxel is supplied in one sterilely sealed vial, a defined solution of anhydrous citric acid (citric acid anhydride) in ethanol (solution A) in a second sterilely sealed vial, and a defined solution of Cremophor EL® or Cremophor ELP® in ethanol (solution B) in a third sterilely sealed vial.

2) Kit according to Claim 1, characterized in that 30 mg, 100 mg, 300 mg, 500 mg, 1000 mg, 2000 mg, 3000 mg, or more of Paclitaxel is supplied in the first vial.

3) Kit according to either Claim 1 or 2, characterized in that solution A consists of 970 mg of anhydrous citric acid (citric acid anhydride) in 70.6 mg of absolute ethanol.

4) Kit according to any one of the preceding Claims 1 through 3, characterized in that solution B consists of 258.8 mg of Cremophor EL ® or Cremophor ELP®, which may be purified by hypercritical fluids if necessary, in 123.5 mg of absolute ethanol.

5) Method for preparing a pharmaceutical formulation of Paclitaxel by dissolving a defined quantity of Paclitaxel in a defined volume of solution A by shaking, and then adding a defined volume of solution B and shaking the mixture until it becomes

homogenous.

6) Method according to Claim 5, characterized in that 3 ml of so lution A and 14 ml of solution B are used per 100 mg of Taxol.

7) Pharmaceutical formulation of Paclitaxel prepared by one of the methods according to

Claims 5 or 6.

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Application No: GB 0207991.1 **Examiner:** Dr William Thomson
Claims searched: 1-7 **Date of search:** 27 August 2003

Patents Act 1977 : Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	1-7	WPI Abstract Accession No 2001-062579/08 & DE 19925211 (PHARMACEUTICAL BULK SUBSTANCES) 12/07/2000 See abstract

Categories

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art
Y	Document indicating lack of inventive step if combined with one or more other documents of same category	P	Document published on or after the declared priority date but before the filing date of this invention
&	Member of the same patent family	E	Patent document published on or after but with priority date earlier than the filing date of this application

Field of Search:

Search of GB. EP WO & US patent documents classified in the following areas of the UKC[1]

Worldwide search of patent documents classified in the following areas of the IPC[7]

A61K

The following online and other databases have been used in the preparation of this search report

CAS-ONLINE, EPODOC, JAPIO, TXTE & WPI